HETEROCYCLES, Vol. 74, 2007, pp. 447 - 459. © The Japan Institute of Heterocyclic Chemistry
Received, 6th August, 2007, Accepted, 20th September, 2007, Published online, 21st September, 2007. COM-07-S(W)23

ELECTROPHILE-INDUCED ETHER TRANSFER: AN EXPEDIENT ROUTE TO 2-CYANO-TETRAHYDROPYRANS

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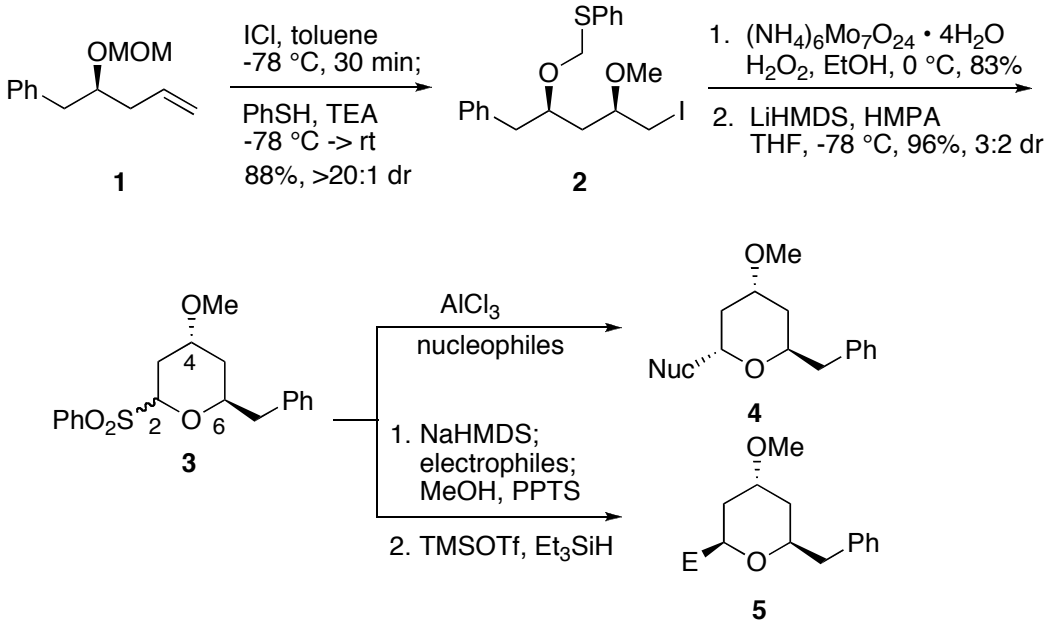
Abstract – Electrophile-induced ether transfer reactions of alkoxymethyl ether protected homoallylic alcohols with cyanide quench provide cyanoether adducts in high yield and excellent 1,3-*syn*-stereoselectivity. Subsequent base-mediated cyclization then provides the corresponding 2,4,6-trisubstituted cyano-tetrahydropyran.

INTRODUCTION

Inspirations for the development of synthetic methodology frequently arise from structural complexity of natural products. For example, Winterfeldt has developed elegant asymmetric cycloaddition reactions via differentiation of enantiotopic groups[1] and utilized this methodology to prepare several biologically active compounds and natural products.[2] In line with this effort, our laboratory has recently developed a new approach to *syn*-diol mono- or diether polyketide synthetic fragments with relative ease from a simple alkoxymethyl ether protected homoallylic alcohol via electrophile-induced ether transfer.[3] As recent extension of this methodology, we then disclosed a stereoselective strategy for the synthesis of 4-alkoxy-2,6-*trans*-tetrahydropyran **4** and its stereocomplementary 2,6-*cis*-tetrahydropyran **5** through a common sulfonyl cyclic ether intermediate **3**, Scheme 1.[4] This intermediate was readily generated in a three-step sequence: iodine monochloride induced ether-transfer reaction of MOM-protected homoallylic **1** with thiophenol – triethylamine quench; second, subsequent oxidation of thioether **2** to its corresponding sulfone using ammonium molybdate – hydrogen peroxide mixture; and finally, LiHMDS-mediated cyclization to arrive at **3**. The 2,6-*trans* stereochemistry was readily accessed by simply treating **3** with $AlCl_3$ and nucleophiles; whereas, 2,6-*cis* was prepared through an alkylation –

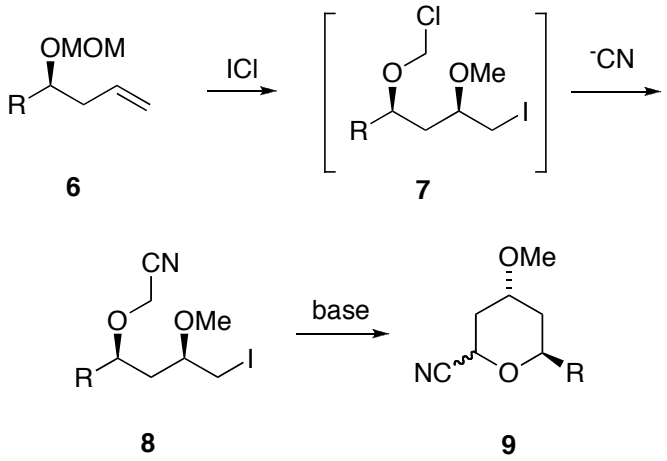
This paper is dedicated to Professor Dr. Ekkhard Winterfeldt on the occasion of his 75th birthday.

reduction sequence. Both tetrahydropyrans **4** and **5** were prepared in high yield and excellent diastereoselectivity using this method.



Scheme 1. 2,4,6-Trisubstituted Tetrahydropyrans via Electrophile-Induced Ether Transfer

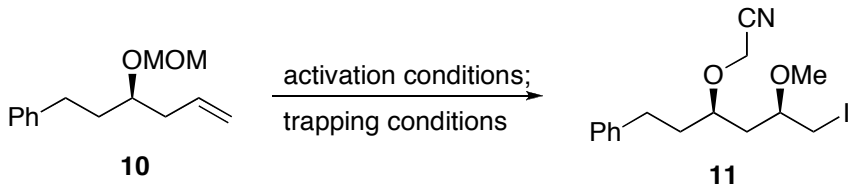
The use of cyano-tetrahydropyran functionality as a key intermediate in total synthesis of polyoxygenated natural products has increased in recent years.[5,8] In this paper, we wish to report an efficient production of stereochemically rich cyano-tetrahydropyrans which provided a complementary strategy to our existing sulfone-based methodology. As shown in Scheme 2, we envisioned trapping the chloromethyl ether intermediate **7** with cyanide ion should provide cyanoether **8** stereoselectively from homoallylic alkoxyether **6**.[6] The presence of cyanide group would then allow deprotonation of the resulting acidic α-proton and cyclization to access cyano-tetrahydropyran **9**.



Scheme 2. General Route to Cyano-Tetrahydropyrans **9**

RESULTS AND DISCUSSION

We began our investigation by realizing that there would be challenges in choosing the appropriate source of cyanide. Some of these challenges included toxicity, solubility, nucleophilicity, and cost-effectiveness of the cyanide source. Cyanotrimethylsilane (TMSCN) would arguably be an excellent source of cyanide for its strong nucleophilicity and high solubility in organic solvents. However, TMSCN becomes unattractive in practice, particularly for a larger scale reaction, due to its considerable toxicity. An alternative and more reasonable source of cyanide ion was then considered, which includes potassium cyanide (KCN), diethylaluminum cyanide (Et_2AlCN), copper cyanide (CuCN), tributyltin cyanide (Bu_3SnCN), and tetraethylammonium cyanide (Et_4NCN). The result of the selection process is presented in Table 1.



10 **11**

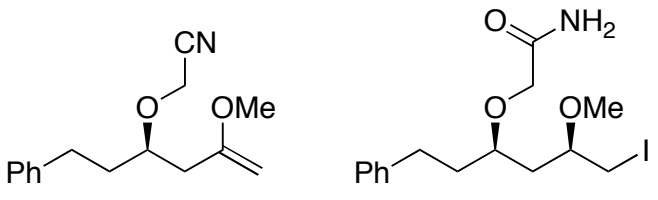
Table 1. Ether Transfer/Cyanide Incorporation

Entry	Activation[a]		Cyanide Source	Quench		Yield[d]	d.r.[e]
	Solvent	Temp (°C)		Solvent[b]	Temp[c] (°C)		
1	toluene	-78	KCN[f,g]	---	-78 → rt	trace	---
2	toluene	-78	Et_2AlCN	toluene	-78 → rt	37%	>20:1
3	1:1 tol/MeCN	-30	Et_2AlCN	toluene	-30 → 0	74%	9:1
4	MeCN	-30	Et_2AlCN	toluene	-30 → 0	57%	2:1
5	toluene	-78	Bu_3SnCN	toluene	-78 → rt	trace	---
6	1:1 tol/MeCN	-30	Bu_3SnCN	toluene	-30 → 0	trace	---
7	toluene	-78	CuCN[f]	---	-78 → 0	decomp.	---
8	toluene	-30	Et_4NCN	1:1 tol/MeCN	-30 → rt	62%	9:1
9	1:1 tol/MeCN	-30	Et_4NCN	1:1 tol/MeCN	-30 → 0	78%	5:1
10	toluene	-78	Et_4NCN	1:1 tol/MeCN	-78 → 0	63%	12:1
11	toluene	-78	Et_4NCN	1:1 tol/MeCN	-78 → rt	62%	12:1
12	toluene	-78 → -30	Et_4NCN	1:2 tol/MeCN	-30	70%	12:1

[a] Conditions in which starting material **10** was activated with ICl. [b] Solvent used to dissolve the cyanide source. [c] Temperature at which cyanide source was introduced to the reaction mixture. [d] Yield isolated as a mixture of diastereomers. [e] Diastereomeric ratio was measured by ^{13}C NMR integration. [f] Cyanide source was added as powder. [g] 18-Crown-6 was employed as an additive.

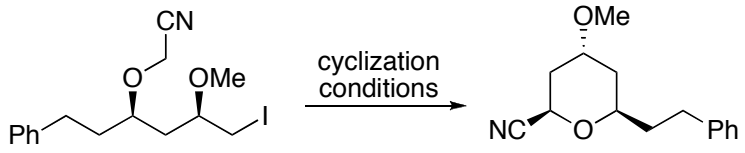
After screening a variety of cyanide sources, it appeared that only the use of Et_2AlCN and Et_4NCN efficiently produced the desired cyanoether adduct **11**. Not surprisingly, the conditions in which MOM-protected homoallylic alcohol **10** was activated with iodine monochloride played a profound role in dictating the diastereoselectivity outcome of the ether-transfer reaction. The diastereoselectivity eroded significantly when activation was performed in more polar solvents. Furthermore, temperature was also found to be crucial. As shown in entries 8 and 10, the diastereoselectivity of the ether-transfer slightly improved from 9:1 at -30 °C to 12:1 at -78 °C. Interestingly, the temperature at which Et_4NCN was introduced to the reaction mixture did not significantly affect the overall quality of the cyanide incorporation process, entries 10-12. The optimized reaction conditions were established with exposure of MOM-protected homoallylic alcohol **10** to ICl in toluene at -78°C followed by warming up the reaction mixture to -30 °C prior to the addition of Et_4NCN. Et_4NCN was introduced as a solution of 1:2 toluene / acetonitrile, and the reaction was stirred at -30 °C for 18 hours.

Table 2 represents optimization efforts to the cyclization of cyanoether **11** to its corresponding cyanopyran **12**. We found that the choice of solvent and base highly influenced the result of this process. For example, deprotonation using NaH in DMF and KO*t*-Bu in THF caused elimination of the primary iodide to vinylether **13**; whereas, amide **14** was formed upon treatment of **11** with KO*t*-Bu in *t*-BuOH, Figure 1. LDA was found unsuitable in this cyclization reaction as only decomposition of starting material was observed. However, the desired cyanopyran **12** was readily generated with lithium hexamethyldisilazide (LiHMDS). As shown in entries 10 and 11, **12** was prepared in high yield as 4:1 mixture of diastereomers (β:α) when cyanoether **11** was reacted with excess LiHMDS – HMPA mixture at -78 °C.



13 **14**

Figure 1. Elimination and Hydration Products



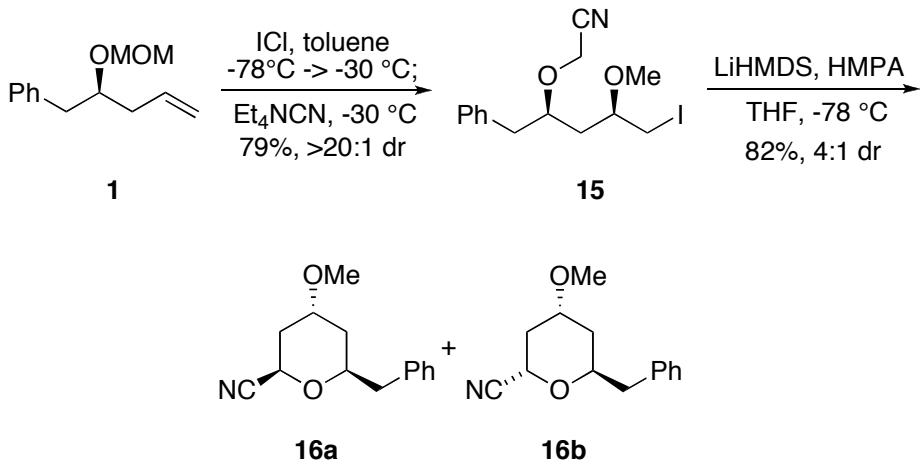
11 **12**

Table 2. Base-Induced Cyclization

Entry	Base	Additive	Solvent	Temp (°C)	Yield[a]	d.r.[b]
1	NaH	---	THF	0 → rt	no reaction	---
2	NaH	---	DMF	0 → rt	elimination[c]	---
3	KO*t*-Bu	---	DMF	0	decomposition	---
4	KO*t*-Bu	---	*t*-BuOH	0 → rt	hydration[d]	---
5	KO*t*-Bu	---	THF	-78 → -20	elimination[c]	
6	LDA	---	THF	-78	decomposition	---
7	LDA	HMPA	THF	-78	decomposition	---
8	NaHMDS	---	THF	-78	trace	1:1
9	LiHMDS	HMPA	THF	-78 → -20	30%	3:1
10	LiHMDS[e]	HMPA[e]	THF	-78	92%	4:1
11	LiHMDS[f]	HMPA[f]	THF	-78	85%	4:1

[a] Yield isolated as a mixture of diastereomers. [b] Diastereomeric ratio was measured by ^{1}H NMR integration. [c] Elimination led to vinylether **13**. [d] Hydration led to amide **14**. [e] 4.0 eq. of LiHMDS and 5.0 eq. of HMPA were employed. [f] 1.5 eq. of LiHMDS and 3.0 eq. of HMPA were employed.

To demonstrate the scalability of this reaction, MOM-protected homoallylic alcohol **1** was subjected to the optimized conditions for both ether-transfer and cyclization reactions in multigram-scale quantity. As shown in Scheme 3, starting with 4.39 grams of **1**, cyanoether product **15** was isolated in 78% yield (5.97 grams) with diastereomeric ratio >20:1. In addition, cyclization of 5.23 grams of **15** proceeded to give cyanopyran **16a** and **16b** in 82% yield (2.76 grams) as 4:1 mixture of diastereomers (**16a**:**16b**). These two diastereomers were separable by column chromatography, and their relative stereochemistry was unambiguously assigned based on ^{1}H NMR coupling constant determination of the relevant protons.



Scheme 3. Gram-Scale Application of Ether-Transfer and Cyclization Reactions

At this point, we envisioned that alkylation of cyanopyran **16** followed by reductive decyanation of subsequent pyran **17** should produce 4-alkoxy-2,6-*cis*-tetrahydropyran **5**. Although pyran **17** could be prepared through alkylation of **16** in high yield, we found that **17** was also conveniently accessible in one step from cyanoether **15** via one-pot cyclization – alkylation reaction. This process included treatment

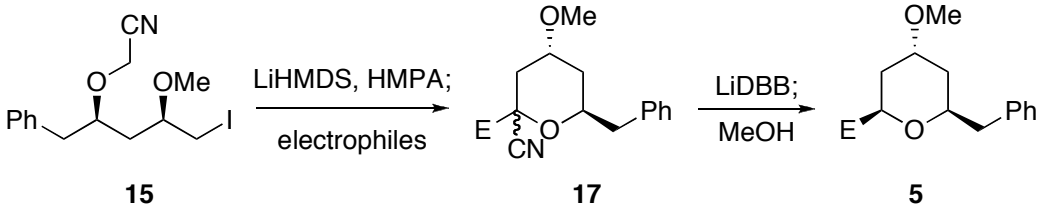
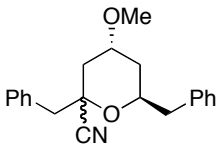
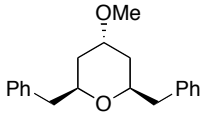
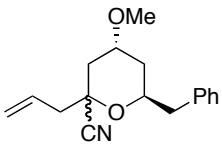
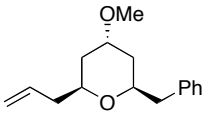


Table 3. One-Pot Cyclization – Alkylation and Reduction Sequence to Tetrahydropyran **5**

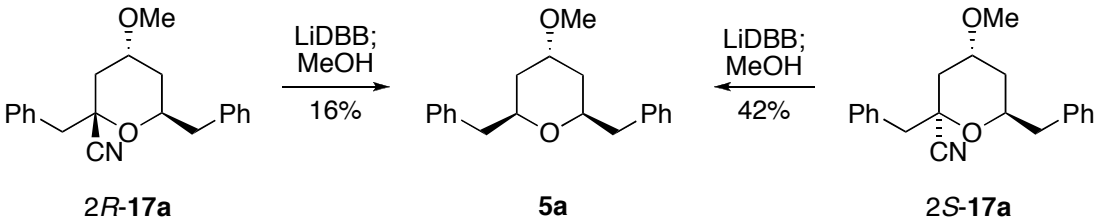
Entry	Electrophile	Alkylation Product **16**	Yield[a]	Reduction Product **5**	Yield[b]
1	benzyl bromide	 **17a**	82% (3:2 d.r.)	 **5a**	47%
2	allyl bromide	 **17b**	95% (3:2 d.r.)	 **5b**	37%

[a] Yield isolated as a mixture of diastereomers. [b] Yield isolated as a single diastereomer. Relative stereochemistry of the ring was determined by ^{1}H NMR coupling constant analysis.

of cyanoether **15** with large excess of LiHMDS followed by a direct addition of electrophiles. In fact, introduction of benzyl bromide and allyl bromide produced **17a** and **17b**, both as a mixture of diastereomer, in 82% and 95% yields respectively.

Initially, we believed that the reductive decyanation step had significant precedent as Rychnovsky has beautifully demonstrated that exposure of cyanopyran and cyanodioxane systems to lithium di-*tert*-butylbiphenylide (LiDBB) cleanly reduced the cyanide group, thus providing tetrahydropyran, dioxane, and spiroannulation products in a stereoselective fashion.[7] This method has been successfully incorporated as the key step in the total synthesis of numerous oxygen-heterocycle containing natural products.[8] However, when LiDBB reduction was applied to cyanopyran **17**, the desired tetrahydropyran **5** was obtained in unsatisfactory yield, Table 3. **5a** was isolated in 47% yield from **17a**, and **5b** in 37% yield from **17b**. The remainder of the crude material was a mixture of unidentifiable compounds. Although Rychnovsky claimed that the stereochemistry of cyanide group does not bear consequences to the reduction process,[9] this conclusion may not be applicable to the 4-alkoxy-substituted systems. To justify this postulation, the two diastereomers of cyanopyran **17a** were then carefully separated by chromatography and then individually exposed to reducing conditions. The stereochemical assignment of each diastereomer was deduced from detailed NMR analyses including ROESY experiment.

Upon exposure to LiDBB, 2*R*-**17a** and 2*S*-**17a** produced **5a** in 16% and 42% yields respectively, Scheme 4. The origin of this observation is not clear to us. The conformational stability and reactivity of anomeric radical in simple tetrahydropyrans and carbohydrates has been thoroughly investigated.[10] However, the stability of 2-tetrahydropyranyl radical bearing 4-alkoxy substituent is not yet well understood. The reactivity differences may well be grounded in their different conformational preferences. We found that based on ^{1}H NMR coupling constant measurement and NOE experiment, 2*R*-**17a** existed in twist-boat conformation, whereas 2*S*-**17a** existed in chair conformation.



2*R*-**17a** **5a** 2*S*-**17a**

Scheme 4. Stereochemical Study

In conclusion, we have developed an efficient, scalable method to access stereochemically rich 2-cyano-tetrahydropyrans via electrophile-induced ether transfer and cyclization. Furthermore, one-pot

cyclization and alkylation of the resulting cyanoether, followed by reductive decyanation and protonation provided 4-alkoxy-2,6-*cis*-tetrahydropyrans. Further optimization of this process and its applications to complex natural product syntheses are currently ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, and diethyl ether (Et_2O) were filtered through activated alumina under nitrogen. Pentane and triethylamine (TEA) was dried over $LiAlH_4$ and CaH_2 respectively, and distilled prior to use. Acetonitrile (MeCN) was dried over 4 Å molecular sieves. 4 Å molecular sieves were oven-dried overnight and then cooled under high vacuum prior to use. All reactions were monitored by Whatman analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230-400 mesh). Biotage chromatography was performed using Flash 40+M, 25+M, 25+S, or 12+M KP-Sil™ Silica (32-63 μm, 60 Å, nominally 500 m^2/g silica) Cartridges. Unless other noted, all ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Varian Unity Plus 500 spectrometers operating at 499.86 MHz for ^1H and 125.69 MHz for ^{13}C. Chemical shifts (δ) were reported in ppm relative to residual $CHCl_3$ as an internal reference (^1H: 7.26 ppm, ^{13}C: 77.00 ppm). Coupling Constant (J) were reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), b (broad), and m (multiplet). FT-IR spectra were recorded on Perkin-Elmer Paragon 1000 spectrometer, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). Mass spectra (FAB) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame, using either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.

(±)-2-((2R,4R)-5-Iodo-4-methoxy-1-phenylpentan-2-yloxy)acetonitrile (15)

MOM-protected homoallylic alcohol **1** (4.39 g, 21.3 mmol) was dissolved in toluene (400 mL), and 4 g of 4 Å molecular sieves was then added. After cooling this solution to -78 °C in an ethanol bath equipped with cryocool apparatus, iodide monochloride solution (25.6 mL, 25.6 mmol, 1M in CH_2Cl_2) was added dropwise while maintaining internal temperature of the reaction below -75 °C. The solution became dark red and was stirred for 30 min while slowly warming up to -30 °C. In a separate flask, tetraethylammonium cyanide (5.00 g, 32.0 mmol) was dissolved in MeCN (40 mL), and 2 g of 4 Å

molecular sieves was added. Toluene (20 mL) was then added which caused the solution to become cloudy. This Et_4NCN solution was added via cannula to the reaction vessel, and the mixture was stirred at -30 °C for 18 h. The reaction was warmed to room temperature and quenched with 200 mL DI water. After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$, and filtered. Removal of solvent under vacuum left behind yellow oil. The crude material was purified with Biotage chromatography to give the title product **15** in 78% yield as yellow oil (5.97 g, 16.6 mmol). Biotage condition: 40+M column, 95:5 hexanes : EtOAc for 120 mL, then 95:5 – 80:20 hexanes : EtOAc linear gradient over 600 mL, then 80:20 hexanes : EtOAc for 240 mL. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.34 – 7.31 (2H, m), 7.27 – 7.21 (3H, m), 4.19 (1H, d, J = 16.5 Hz), 4.06 (1H, d, J = 16.5 Hz), 3.81 (1H, p, J = 6.0 Hz), 3.36 (1H, dd, J = 19.5, 5.5 Hz), 3.33 (3H, s), 3.29 (1H, dd, J = 11.0, 3.5 Hz), 3.10 (1H, m), 2.90 (1H, dd, J = 14.0, 6.5 Hz), 2.84 (1H, dd, J = 13.5, 5.5 Hz), 1.86 – 1.83 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.11, 129.35, 128.53, 126.68, 116.32, 79.02, 76.07, 56.64, 54.60, 40.46, 38.63, 9.57. IR (cm^{-1}): 3062, 3028, 2926, 2825, 2191, 1603, 1496, 1454, 1348, 1273, 1182, 1087, 888, 748, 702. HRMS-FAB $(M+H)^+$ = 360.0461 calculated for $C_{14}H_{19}O_2NI$, experimental = 360.0466.

(±)-(4R,6R)-6-Benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carbonitrile (16)

HMDS (4.64 mL, 21.8 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. A solution of *n*-BuLi (9.50 mL, 21.8 mmol, 2.3 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 10 min prior to addition of HMPA (7.60 mL, 43.7 mmol). This LiHMDS solution was further stirred for 10 min. In a separate flask, cyanoether **15** (5.23 g, 14.6 mmol) was dissolved in THF (300 mL), and the solution was cooled to -78 °C. The freshly prepared, cold LiHMDS solution was then added via cannula dropwise over 30 min. The reaction was further stirred for 2 h and then quenched with half-saturated aqueous NH_4Cl solution (200 mL). After warming up rt, the organic and aqueous layers were separated. The aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under vacuum leaving behind dark orange oil. The crude material was purified with Biotage chromatography to give title product **16** in 82% yield as yellow oil (2.76 g, 11.9 mmol). Crude ^{1}H NMR indicated 4:1 diastereomeric ratio. Biotage condition: 40+M column, 90:10 hexanes : EtOAc for 240 mL, then 90:10 – 70:30 hexanes : EtOAc linear gradient over 720 mL, then 70:30 hexanes : EtOAc for 120 mL.

The less polar (major) diastereomer **16a**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.28 (2H, m), 7.24 – 7.19 (3H, m), 4.60 (1H, dd, J =12.5, 2.5 Hz), 3.29 (1H, dddd, J = 13.5, 6.5, 6.5, 2.0 Hz), 3.67 (1H, p, J = 3.0 Hz), 3.27 (3H, s), 2.89 (1H, dd, J = 14.0, 7.0 Hz), 2.67 (1H, dd, J = 14.0, 6.0 Hz), 2.09 (1H, dddd, J = 14.0, 5.5, 2.5, 2.5 Hz), 1.91 (1H, ddd,

J = 14.0, 12.5, 3.0 Hz), 1.80 (1H, dddd, J = 14.5, 3.0, 2.0, 2.0 Hz), 1.42 (1H, ddd, J = 14.0, 11.5, 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.39, 129.44, 128.29, 126.44, 118.54, 73.85, 71.56, 61.31, 56.14, 42.04, 33.76, 33.43. IR (cm^{-1}): 3021, 2924, 2879, 2826, 1603, 1449, 1342, 1183, 1086, 1070. HRMS-FAB $(M+H)^+$ = 232.1338 calculated for $C_{14}H_{18}O_2N$, experimental = 232.1325.

The more polar (minor) diastereomer **16b**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.28 (2H, m), 7.23 – 7.20 (3H, m), 4.77 (1H, dd, J = 6.0, 0.5 Hz), 4.41 (1H, dddd, J = 13.0, 6.5, 6.5, 2.0 Hz), 3.67 (1H, p, J = 3.0 Hz), 3.36 (3H, s), 2.88 (1H, dd, J = 14.0, 7.0 Hz), 2.74 (1H, dd, J = 14.0, 6.0 Hz), 2.15 (1H, m), 1.89 (1H, m), 1.88 (1H, ddd, J = 15.0, 6.5, 3.0 Hz), 1.47 (1H, ddd, J = 14.5, 12.0, 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.11, 129.30, 128.35, 126.43, 118.67, 71.00, 69.59, 60.90, 56.01, 41.80, 34.54, 30.03. IR (cm^{-1}): 3030, 2924, 2826, 1599, 1449, 1369, 1342, 1187, 1086, 1028. HRMS-FAB $(M+H)^+$ = 232.1338 calculated for $C_{14}H_{18}O_2N$, experimental = 232.1355.

General Procedure A: *One-Pot Cyclization and Alkylation*

HMDS (1.42 mL, 6.68 mmol) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *n*-BuLi (2.90 mL, 6.68 mmol, 2.3 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 15 min prior to addition of HMPA (1.45 mL, 8.35 mmol). This LiHMDS solution was further stirred for 30 min. In a separate flask, cyanoether **15** (300 mg, 0.835 mmol) was dissolved in THF (20 mL), and the solution was cooled to -78 °C in an ethanol bath equipped with cryocool apparatus. The freshly prepared, cold LiHMDS solution was then added via cannula dropwise. The reaction was further stirred for 15 min and then alkylating agent (4.18 mmol) was added dropwise. The reaction was then warmed up to -30 °C and stirred overnight. Half-saturated NH_4Cl (50 mL) was then added in one portion, and the mixture was warmed up to room temperature. The organic and aqueous layers were separated. The aqueous layer was washed with Et_2O (2 x 20 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under vacuum leaving behind yellow oil. The crude material was purified with Biotage chromatography to give title product **16** as a mixture of diastereomers. Biotage condition: 25+M column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 – 80:20 hexanes : EtOAc linear gradient over 360 mL, then 80:20 hexanes : EtOAc for 90 mL.

(±)-(4R,6R)-2,6-Dibenzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carbonitrile (17a)

General Procedure A was followed. Benzyl bromide (0.497 mL, 4.18 mmol) was employed as the alkylating agent. Title product **17a** was isolated in 82% yield with diastereomeric ratio of 3:2 as yellow oil (221 mg, 0.688 mmol).

The less polar (major) diastereomer 2*R*-**17a**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32 – 7.28 (2H, m), 7.27 – 7.21 (6H, m), 7.18 – 7.16 (2H, m),

4.26 (1H, m), 3.80 (1H, m), 3.39 (1H, d, J = 14.0 Hz), 3.34 (3H, s), 3.04 (1H, d, J = 14.0 Hz), 3.01 (1H, dd, J = 13.5, 6.5 Hz), 2.83 (1H, dd, J = 13.5, 6.0 Hz), 2.16 (1H, dd, J = 14.0, 4.5 Hz), 1.98 (1H, dd, J = 14.0, 6.0 Hz), 1.78 – 1.75 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.77, 134.36, 130.53, 129.51, 128.37, 128.20, 127.17, 126.43, 121.05, 73.05, 71.66, 70.58, 56.19, 43.45, 41.49, 36.68, 33.05. IR (cm^{-1}): 3030, 2929, 2832, 1497, 1455, 1199, 1077, 1048. HRMS-FAB $(M\cdot)^+$ = 321.1729 calculated for $C_{21}H_{23}O_2N$, experimental = 321.1730.

The more polar (minor) diastereomer 2*S*-**17a**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.29 – 7.27 (7H, m), 7.23 – 7.19 (3H, m), 4.38 (1H, dddd, J = 12.5, 6.5, 6.5, 2.0 Hz), 3.63 (1H, p, J = 3.0 Hz), 3.29 (3H, s), 3.10 (1H, d, J = 13.5 Hz), 3.01 (1H, d, J = 13.5 Hz), 2.90 (1H, dd, J = 14.0, 6.5 Hz), 2.76 (1H, dd, J = 14.0, 6.0 Hz), 2.15 (1H, ddd, J = 14.5, 2.0, 2.0 Hz), 1.86 (1H, dddd, J = 14.0, 3.0, 2.0, 2.0 Hz), 1.55 (1H, dd, J = 14.5, 3.0 Hz), 1.36 (1H, ddd, J = 14.0, 11.5, 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.32, 133.74, 130.79, 129.48, 128.22, 128.17, 127.37, 126.30, 120.04, 71.73, 71.62, 70.56, 56.02, 47.34, 41.82, 35.56, 34.02. IR (cm^{-1}): 3027, 2925, 1497, 1455, 1100, 1074, 1042. HRMS-FAB $(M\cdot)^+$ = 321.1729 calculated for $C_{21}H_{23}O_2N$, experimental = 321.1729.

(±)-(4R,6R)-2-Allyl-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carbonitrile (17b)

General Procedure A was followed. Allyl bromide (0.364 mL, 4.18 mmol) was employed as the alkylating agent. Title product **17b** was isolated in 95% yield with diastereomeric ratio of 3:2 as yellow oil (215 mg, 0.792 mmol).

The less polar (major) diastereomer 2*R*-**17b**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.28 (2H, m), 7.24 – 7.20 (3H, m), 5.73 (1H, dddd, J = 17.0, 10.5, 7.0, 7.0 Hz), 5.19 – 5.15 (2H, m), 4.11 (1H, dddd, J = 10.0, 7.0, 7.0, 3.5 Hz), 3.74 (1H, m), 3.30 (3H, s), 2.98 (1H, dd, J = 13.5, 7.0 Hz), 2.93 (1H, dd, J = 14.5, 7.0 Hz), 2.80 (1H, dd, J = 14.0, 6.5 Hz), 2.54 (1H, dd, J = 14.0, 7.5 Hz), 2.12 (1H, dd, J = 14.5, 4.0 Hz), 1.97 (1H, ddd, J = 14.0, 5.5, 1.0 Hz), 1.73 (1H, dddd, J = 14.0, 5.0, 3.5, 1.0 Hz), 1.70 (1H, ddd, J = 13.0, 9.0, 3.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.75, 131.03, 129.42, 128.30, 126.39, 121.05, 120.08, 72.29, 71.79, 69.92, 56.18, 41.56, 41.47, 35.88, 33.12. IR (cm^{-1}): 3084, 3029, 2929, 2830, 1644, 1605, 1497, 1455, 1350, 1201, 1079, 1045, 924, 751, 701. HRMS-FAB $(M-H)^+$ = 270.1494 calculated for $C_{17}H_{20}O_2N$, experimental = 270.1522.

The more polar (minor) diastereomer 2*S*-**17b**:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.30 – 7.26 (2H, m), 7.23 – 7.20 (3H, m), 5.87 (1H, dddd, J = 17.0, 10.5, 7.5, 7.0 Hz), 5.25 – 5.20 (2H, m), 4.37 (1H, dddd, J = 12.0, 6.0, 6.0, 2.0 Hz), 3.65 (1H, p, J = 2.5 Hz), 3.33 (3H, s), 2.90 (1H, dd, J = 13.5, 6.0 Hz), 2.74 (1H, dd, J = 14.0, 6.0 Hz), 2.56 (1H, dddd, J =

14.0, 7.0, 5.5, 5.5 Hz), 2.48 (1H, dddd, J = 14.0, 7.5, 1.0, 1.0 Hz), 2.21 (1H, ddd, J = 14.5, 3.0, 2.0 Hz), 1.86 (1H, ddd, J = 14.0, 3.5, 2.0, 2.0 Hz), 1.52 (1H, dd, J = 14.5, 3.0 Hz), 1.36 (1H, ddd, J = 14.0, 11.5, 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 137.26, 130.46, 129.49, 128.19, 126.31, 120.38, 120.11, 71.66, 70.87, 70.47, 55.98, 45.85, 41.79, 35.52, 34.02. IR (cm^{-1}): 3084, 3028, 2926, 2828, 1644, 1605, 1455, 1348, 1196, 1099, 1083, 924, 744, 701. HRMS-FAB $(M-H)^+$ = 270.1494 calculated for $C_{17}H_{20}O_2N$, experimental = 270.1499.

General Procedure B: *Reductive Decyanation Using LiDBB*

In a pear-shaped flask, cyanopyran **17** (1.0 equivalent) as a mixture of diastereomers was dissolved degassed THF (10 mL). 200 mg of 4 Å molecular sieves was then added. After standing for 10 min, this solution was then transferred to a round-bottomed flask via cannula. To ensure cyanopyran **17** was completely transferred, the pear-shaped flask was washed with THF (2 x 2.5 mL) and transferred via cannula. This solution was then cooled to -78 °C. A freshly prepared solution of LiDBB (2.5 equivalents, 0.4 M in THF) was then added dropwise. Toward the end of LiDBB addition, the reaction mixture turned dark green. After stirring for 30 min, MeOH (2 mL) was added dropwise causing the green color to disappear. The mixture was warmed to rt and diluted with half-saturated NH_4Cl solution (20 mL). The organic and aqueous layers were separated. The aqueous layer was washed with Et_2O (2 x 20 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under vacuum leaving behind yellow oil. Column chromatography purification with silica gel and 95:5 hexanes : EtOAc solvent system provided title product **5**.

(2S,4S,6R)-2,6-Dibenzyl-tetrahydro-4-methoxy-2*H*-pyran (5a)

General Procedure B was followed. Cyanopyran **17a** (150 mg, 0.467 mmol) and LiDBB (2.93 mL, 1.17 mmol, 0.4 M in THF) were employed, and tetrahydropyran **5a** was isolated in 47% yield (65.0 mg, 0.219 mmol) as colorless oil. Spectroscopic analyses of **5a** was identical to previously reported data.[4]

(±)-(2S,4S,6R)-2-Allyl-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran (5b)

General Procedure B was followed. Cyanopyran **17b** (180 mg, 0.663 mmol) and LiDBB (4.15 mL, 1.66 mmol, 0.4 M in THF) were employed, and tetrahydropyran **5b** was isolated in 37% yield (60.0 mg, 0.244 mmol) as colorless oil. Spectroscopic analyses of **5b** was identical to previously reported data.[4]

ACKNOWLEDGEMENTS

Support provided by the National Institutes of Health through the National Institute of General Medical Science (GM077683) is gratefully acknowledged.

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